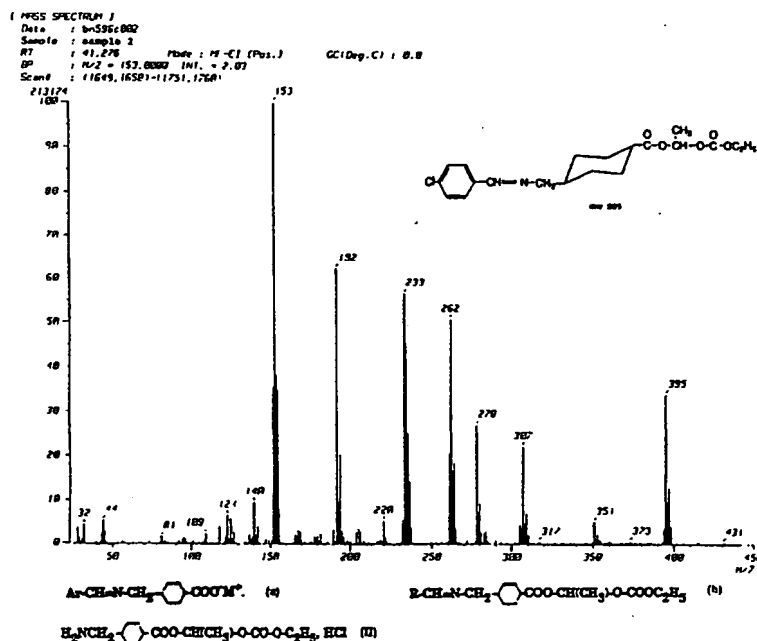




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(54) Title: NOVEL PROCESS AND INTERMEDIATES FOR THE PREPARATION OF PRODRUGS



(57) Abstract

A tranexamic acid prodrug of general formula (II), is prepared by conversion of tranexamic acid in aqueous solution into a salt. An aromatic aldehyde of the formula Ar-CHO, lacking α -hydrogen atom is added to the solution and water is removed so as to form a salt of formula (a). The obtained suspension of anhydrous N-substituted tranexamic acid salt is esterified with 1-halogenethyl ethyl carbonate, wherein the halogen is chloro or bromo, and the halogenide formed and possibly present catalyst are removed. Protected esters of formula (b) wherein R signifies phenyl or naphthyl which may be substituted with lower alkyl or lower alkoxy groups or halogen atoms, are novel intermediates which can be used for the preparation of the prodrug (II).

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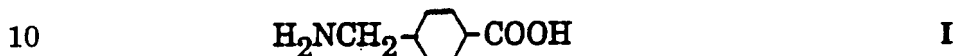
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GA	Gabon				

Novel process and intermediates for the preparation of prodrugs.Field of the invention.

The present invention relates to a novel process and to novel chemical intermediates for preparing derivatives, or prodrugs, of tranexamic acid which is a well known and effective antifibrinolytic drug. It is widely used clinically and is available from e.g. Kabi Pharmacia AB under the trademark Cyklokapron®.

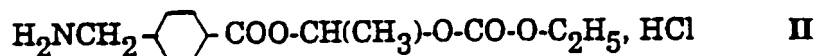
Background of the invention

Tranexamic acid, i.e. trans-4-aminomethylcyclohexanecarboxylic acid, has the chemical structure I.



The bio-availability of tranexamic acid is, however, fairly low. On oral administration only about 30-40% of the drug is absorbed and a considerable amount is excreted in the faeces. This may cause undesired gastrointestinal side effects in some patients.

15 Attempts have been made to overcome these disadvantages. For example, EP-A-0079872 discloses several ester derivatives (so-called prodrugs) of tranexamic acid. These ester derivatives have a high bioavailability and are rapidly metabolized to tranexamic acid in the human body. Of the specific ester derivatives disclosed in EP-A-0079872, 1-(ethyloxy-carbonyloxy)ethyltrans-4-aminomethylcyclohexane-
20 carboxylate-hydrochloride (formula II) has been selected for clinical studies and found to fulfill the expectations. See J.Med.Chem. 1986 29, 448-453, and Arz-
neim.-Forsch. 1988 38, 735-738.



EP-A-0079872 discloses the following methods for preparing the compound of
25 formula II:

a) Reacting a compound of Formula III



wherein Z^1 and Z^2 are hydrogen or protecting groups,
or a functionally equivalent derivative thereof such as a salt,
with a compound of Formula IV



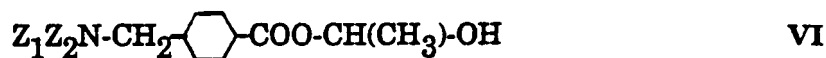
- 5 or a functionally equivalent derivative thereof, to form a compound of Formula V,



wherein Z^1 and Z^2 are as defined above.

- If necessary, the protecting groups Z^1 and Z^2 are removed so as to form the com-
10 pound of Formula II,

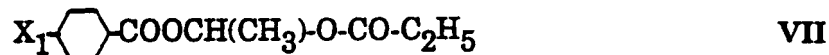
b) Reacting a compound of Formula VI



wherein Z^1 and Z^2 are as defined above,

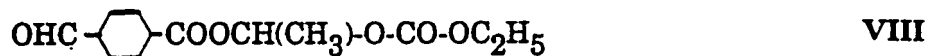
- or a functionally equivalent derivative thereof,
15 with a compound $\text{HO-CO-OC}_2\text{H}_5$ or a functionally equivalent derivative thereof,
so as to form the above compound of Formula V.

c) Reducing a compound of the Formula VII



- wherein X^1 is $-\text{CN}$, $-\text{CH}_2\text{NO}_2$, $-\text{CH}_2\text{N}_3$, $-\text{CONH}_2$, or $-\text{CH=NOH}$,
20 so as to form the compound of Formula II.

d) Reducing a compound of the Formula VIII



in the presence of ammonia and subsequent treatment with hydrogen chloride so

as to form the compound of Formula II.

All of the above described, previously known methods have certain disadvantages. For example, the method d) gives rise to a mixture of cis- and trans-forms of the product, which has to be separated. Because of the delicate nature of the pro-drug
5 II (the compound is sensitive to both high and low pH, and especially to high temperatures) this is an arduous task, especially on a commercial scale.

The method c) has the disadvantage that the starting materials are not available on a technical scale, especially not as pure trans-forms, so complicated procedures are required for preparing them.

- 10 In the method a) the starting material is tranexamic acid which, as such or after proper protection of the amino group, is esterified to the pro-drug of Formula II or its protected derivative of Formula V, which then is deprotected. The method b) is similar, but the esterification is carried out in two steps via the intermediate of Formula VI.
- 15 EP-A-0079872 does not disclose any example, wherein the unprotected tranexamic acid is used in the process, and experiments have shown that only marginal yields of a highly contaminated material can be obtained when using this starting material.

On page 9 EP-A-0079872 generally states that the protecting groups Z_1 and Z_2
20 preferably are groups which can be removed under neutral or acidic conditions or by hydrogenation, especially catalytic hydrogenation. Tert.-butoxycarbonyl, benzyloxycarbonyl, dibenzyl, triphenylmethyl, alkylcarbonyl and arylcarbonyl are mentioned as examples of such groups, but only tert.-butoxycarbonyl is used in the working examples.

- 25 All of the protecting groups mentioned in EP-A-0.079.872 require a separate reaction step for the preparation and isolation of the protected tranexamic acid (Formula III above). With the exception of alkylcarbonyl and arylcarbonyl, the raw materials used for the protecting groups are also rather expensive. Simple representatives of alkylcarbonyl and arylcarbonyl protecting groups such as acetyl
30 or benzoyl are, however, much too resistant to hydrolysis to allow their removal

from the protected ester of Formula V without extensive destruction of the intermediate of formula VI and the desired product of Formula II. Use of protecting groups, which are removed by catalytic hydrogenation, is also disadvantageous since it requires special equipment and precautions for handling of hydrogen.

It is obvious from the above that an improved method, which permits conversion of tranexamic acid to the prodrug of Formula II without requiring isolation of any intermediate(s) and which makes use of inexpensive, commercially available starting materials for the protecting group, would be highly desirable.

Summary of the invention

According to the invention, it has surprisingly been found, that the desired prodrug of Formula II as its hydrochloride can be prepared from tranexamic acid of Formula I in a simple and straight-forward reaction sequence using commercially readily available and inexpensive aldehydes, such as benzaldehyde, or similar aldehydes lacking an α -hydrogen atom, such as alkyl-, alkoxy- or halogen-substituted benzaldehydes or naphthaldehydes, for the protection of the amino group, and that the invented process can be carried out in one sequence without isolation of any intermediates. The reaction sequence can, however, also be carried out such that novel chemical intermediates are isolated (for subsequent conversion to the prodrug of formula II). Such chemical intermediates are also comprised by the invention.

The prodrug of Formula II is a sensitive substance which in aqueous solution has satisfactory stability only in the pH range from about 1 to about 7 and at low temperatures. The success of the process therefore depends on a delicate balance between the stability of the protecting group during the reactions in organic solvents and its ease of removal by acid hydrolysis in aqueous solution after the esterification has taken place. According to the invention this balance is obtained by the use of the herein specified aldehydes lacking α -hydrogen atoms - which with tranexamic acid form Schiff's bases, that are stable during the esterification at elevated temperatures. Other aldehydes, which undergo aldol condensation under the said conditions, are not useful according to the invention.

In one aspect the invention thus provides an improved process for preparing

tranexamic acid prodrugs. The process according to the invention thus involves the following steps, which can be carried out either in sequence without isolation of any intermediate or with isolation of the novel ester intermediates according to the invention which are obtained in step 3 below.

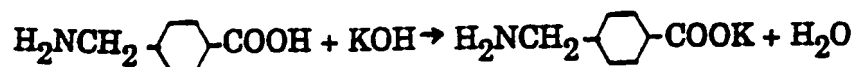
5 1. Conversion of tranexamic acid of formula I



into a salt $\text{H}_2\text{NCH}_2\text{---}\langle\text{cyclohexane ring}\rangle\text{---COO}^-\text{M}^+$

wherein M^+ is a salt forming ion such as an alkali metal ion, quaternary ammonium ion or possibly alkaline earth ion.

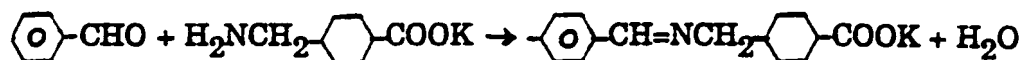
- 10 It is preferred to convert the tranexamic acid to a potassium salt, e.g. as illustrated by the following equation:



2. Addition of an aldehyde of the formula Ar-CHO to the solution, said aldehyde Ar-CHO being an aromatic aldehyde, e.g. a benzaldehyde or naphthaldehyde lacking α -hydrogen atom and preferably being substituted by alkyl or alkoxy groups or halogen atoms, and removal of water from the resulting solution of N-substituted tranexamic acid (preferably N-benzylidenetranexamic acid) by azeotropic distillation, preferably with a solvent which is not miscible with water but is capable of forming azeotropes with water boiling in the range between 40-150°C to form a salt of the Formula



This reaction can be illustrated as follows for the preferred benzaldehyde:

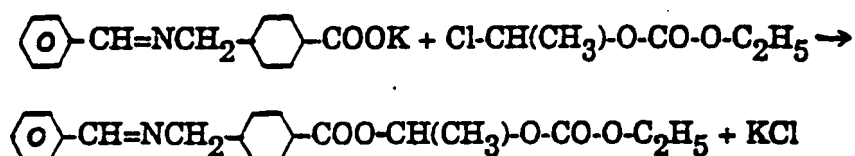


3. Esterification of the suspension of anhydrous N-substituted tranexamic acid salt thus obtained with 1-halogenethyl ethyl carbonate, wherein the halogen is

chloro or bromo, preferably in the presence of a catalytic amount of a quaternary ammonium salt such as tetrabutylammonium bromide, especially when the halogen is chloro, at an elevated temperature, preferably between 30 and 110°C.

This esterification can be illustrated as follows for the preferred N-benzylidene tranexamic acid:

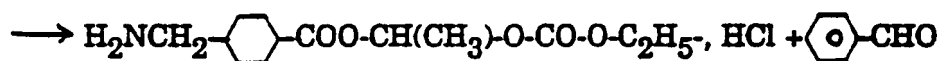
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4. Removal of the halogenide formed and the catalyst, e.g. by washing with water after cooling, preferably below room temperature and especially below 10°C.

5. Optional treatment of the solution of the N-substituted tranexamic ester thus obtained with a slight excess of dilute aqueous hydrochloric acid, preferably 0.1-1 molar and preferably below 10°C in order to hydrolytically remove the protecting group. This step can be illustrated as follows:

10



6. Optional washing of the resulting aqueous solution of prodrug II with a solvent, preferably the same as used in steps 2 to 5 in order to remove dissolved benzaldehyde, and isolation of the product in crystalline form by cautious evaporation, e.g. by thin film evaporation, spray-drying or freeze drying or combinations thereof, or by extraction with an organic solvent such as dichloromethane.

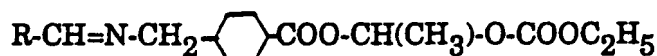
15

Instead of potassium hydroxide other water soluble bases such as sodium hydroxide, lithium hydroxide or calcium hydroxide, or a quaternary ammonium hydroxide can be used.

20 Instead of benzaldehyde other aldehydes as defined above can be used. Instead of toluene or trichloroethylene other solvents not miscible with water but forming azeotropes with water boiling in the range between 40-150°C can be used, toluene and trichloroethylene being, however, the preferred solvents.

The end product obtained is of satisfactory purity to be processed into tablets without further purification, but it may, if desired, be further purified by recrystallisation, e.g. from a mixture of 2-propanol and light petrol.

- In another aspect the invention also provides novel chemical intermediates useful for preparing the prodrug of formula II. A preferred group of such intermediates are protected esters which can be represented by the following formula:



- wherein R signifies phenyl or naphthyl which may be substituted with lower alkyl or lower alkoxy groups or halogen atoms, said lower alkyl and lower alkoxy groups comprising 1 to 6 carbon atoms, preferably 1 to 3 carbon atoms.

- As mentioned above these intermediates can be isolated by interrupting the reaction sequence after the esterification step. The novel intermediates are usually oils which are rather stable if stored at a temperature below room temperature, preferably below 10°C. Characterizing data for some intermediates are shown in the enclosed Figures 1-4.

- The use of Schiff's bases from aldehydes as protecting groups for amines in organic synthesis, is well known. (See e.g. T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York 1981, 275-279, Houben-Weyl Methoden der organischen Chemie, Band 15:1 pp. 277-285, 295-297. Georg Thieme Verlag, Stuttgart 1974.) Schiff's bases with unsubstituted aldehydes like benzaldehydes are, however, generally considered to be too unstable to be of more general value and aromatic aldehydes containing an ortho hydroxy group, which stabilizes the Schiff's base by hydrogen bond formation, or a β-discarbonyl compound such as ethyl acetoacetate, which form hydrogen bond stabilized enamines, are generally preferred.

- The initial experiments leading to the present invention were therefore carried out with such hydrogen bond forming protective groups. These derivative of II were, however, found to be too stabile in the hydrolysis step to allow the isolation of the desired compound II in high yield and purity. The use of β-discarbonyl compounds like ethyl acetoacetate was also hampered by the fact that the

protected I was too unstable thermally to function satisfactorily in the esterification step, again resulting in low yields and impure products.

It was therefore entirely unexpected that the simple aldehydes which are used according to the invention, especially unsubstituted benzaldehyde, an inexpensive and readily available commercial product, proved to be ideal for the purposes of the invention.

Example 1

1-(Ethyloxycarbonyloxy)ethyl trans-4-aminomethyl cyclohexane carboxylate hydrochloride

10 Potassium hydroxide (88%, 12% water) 638 g (10.0 mol) is dissolved in 500 ml of water. Tranexamic acid (1572 g; 10.0 mol) is added with stirring. The clear solution formed is chilled to about 50°C and benzaldehyde (1114 g; 10.5 mol) is added with stirring. A precipitate forms which rapidly goes into solution. Toluene (10 l) is added and the mixture is stirred and boiled with continuous separation of
15 water by azeotropic distillation. A sticky, jellied mass is formed which, as the water is removed, is converted into a suspension of fine needle-like, colorless crystals of potassium trans-4-benzylideneiminomethyl-cyclohexane-carboxylate.

The mixture is chilled to 40-60°C, tetrabutylammonium bromide (323 g; 1.0 mol) is added followed by 1-chlorethyl ethyl carbonate (1602 g; 10.5 mol) and the
20 mixture is stirred for 4-5 hours at 55-65°C. The solid salt gradually passes into solution and is replaced by a jellylike precipitate of potassium chloride. The mixture is chilled to below 10°C and rapidly washed with three 7 l portions of ice cold water. The toluene phase containing the 1-(ethyloxycarbonyloxy)ethyl trans-4-benzylideneiminomethyl cyclohexane carboxylate is separated, mixed with
25 5 l of ice cold water, and treated with rapid stirring below 10°C with a 1 molar solution of hydrochloric acid added at such a rate that the pH of the mixture is kept at about 1.2 to 1.8 (a total amount of about 10 l is required). The aqueous phase is separated and repeatedly washed with cold toluene to remove benzaldehyde and traces of neutral impurities yielding an aqueous solution of 1-(ethyloxycarbonyloxy)ethyl trans-4-aminomethyl cyclohexane carboxylate hydrochloride
30 containing a small amount of unreacted tranexamic acid, usually less than 2%. The product is isolated from this solution by rapid evaporation of the water at

below 30°C in a vacuum, which gives an oil that sets into a crystalline mass, or by spray drying. The yield of product of about 99% purity is about 84%. If desired, the product can be purified by dissolution in hot 2-propanol and precipitation with petrol. The melting point of the recrystallized product is 142°C.

5

Example 2

1-(Ethyloxycarbonyloxy)ethyl trans-4-aminomethyl cyclohexane carboxylate hydrochloride

A suspension of potassium trans-4-benzylidene iminomethyl cyclohexane carboxylate in trichloroethene is prepared following the directions of Example 1 but using
10 10 l of trichloroethene instead of toluene. The salt is esterified by stirring overnight with 1-bromoethyl ethyl carbonate (2068 g; 10.5 mol) at 30-40°C. The reaction mixture is worked up and the product is isolated as described in Example 1. The yield of product of 98% purity is 85%.

Example 3

15 Preparation of N-substituted 1-(ethyloxycarbonyloxy)ethyl trans-4-iminomethyl cyclohexane carboxylates

a) 1-(Ethyloxycarbonyloxy)ethyl trans-4-benzylideneiminomethyl cyclohexane carboxylate

A mixture of potassium hydroxide (88%; 12.8 g; 0.20 mol), tranexamic acid (31.4 g;
20 0.20 mol), and water (50 ml) is stirred until a clear solution is obtained. Benzaldehyde (21.2 g; 0.20 mol) is added and the mixture is stirred until a clear solution is again obtained. The solution is evaporated to dryness in vacuum on a water bath. Toluene (500 ml) is added and the last traces of water are removed by azeotropic distillation. Tetrabutylammonium bromide (3.2 g; 0.010 mol) and 1-
25 chloroethyl ethyl carbonate (32.0 g; 0.21 mol) are added and the mixture is stirred and heated at 50-60°C for 5 hours. It is poured into iced water and repeatedly washed with cold water, dried over anhydrous sodium sulphate, and evaporated in vacuum below 30°C. An oil, 77 g, is obtained that according to gas chromatography is 92% pure. Yield 98%. The identity of the compound was confirmed by
30 gas chromatography-mass spectroscopy.

- b) 1-(Ethyloxycarbonyloxy)ethyl trans-4-(4-chlorobenzylideneimino)methyl-cyclohexanecarboxylate

This compound is analogously prepared from 4-chlorobenzaldehyde. The compound is obtained in 88% purity and 83% yield.

- 5 c) 1-(Ethyloxycarbonyloxy)ethyl trans-4-(4-methylbenzylideneimino)methyl-cyclohexanecarboxylate

This compound is analogously prepared from 4-methylbenzaldehyde. Purity 76%, yield 68%.

- 10 d) 1-(Ethyloxycarbonyloxy)ethyl trans-4-(2-methoxybenzylideneimino)methyl-cyclohexanecarboxylate

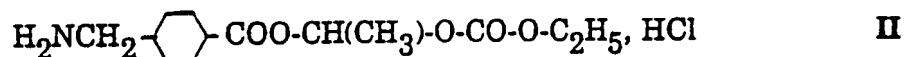
This compound is analogously prepared from 2-methoxybenzaldehyde. Purity 83%, yield 70%.

- e) 1-(Ethyloxycarbonyloxy)ethyl trans-4-(1-naphtylmethyleneimino)methyl-cyclohexanecarboxylate

- 15 This compound was analogously prepared from 1-naphtaldehyde. Purity 65%, yield 57%.

CLAIMS

1. An improved process for preparing a tranexamic acid prodrug of the general formula II,



characterized in that it comprises the following steps:

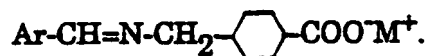
- 5 a) conversion of tranexamic acid of formula I in aqueous solution



into a salt $\text{H}_2\text{NCH}_2-\text{C}_6\text{H}_{10}-\text{COO}^-\text{M}^+$

wherein M^+ is a salt forming ion,

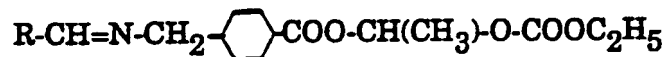
- b) addition of an aromatic aldehyde of the formula $\text{Ar}-\text{CHO}$ to the solution, said aldehyde lacking α -hydrogen atom, and removal of water from the resulting
10 solution of N-substituted tranexamic acid to form a salt of the Formula



- c) esterification of the suspension of anhydrous N-substituted tranexamic acid salt thus obtained with 1-halogenethyl ethyl carbonate, wherein the halogen is chloro or bromo, preferably in the presence of a catalytic amount of a quaternary ammonium salt,
15 d) removal of the halogenide formed and possibly present catalyst, and
e) treatment of the solution of the N-substituted tranexamic ester thus obtained with a slight excess of dilute aqueous hydrochloric acid.

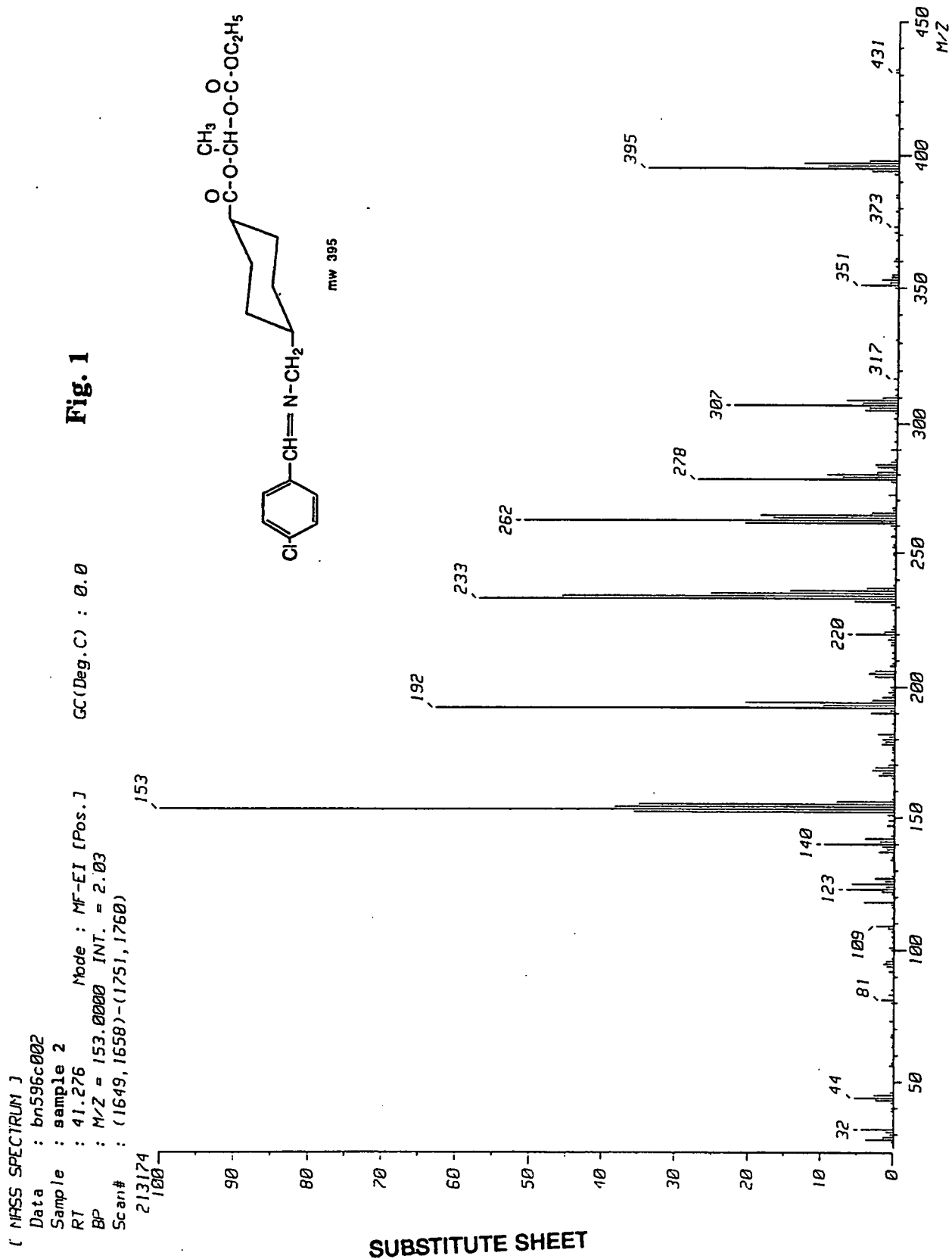
2. The process of claim 1, characterized in that the aldehyde $\text{Ar}-\text{CHO}$ is a benzaldehyde or naphthaldehyde, which may be substituted by alkyl or alkoxy
20 groups or halogen atoms, that the salt forming ion M^+ is an alkali metal ion or a quaternary ammonium ion and that water is removed by azeotropic distillation.

3. The process of claim 1 or 2, **characterized in** that the protected ester obtained is isolated before removal of the protecting group.
4. Novel chemical intermediates useful for preparing the prodrug of formula II, **characterized in** that they are protected esters which can be represented by
- 5 the following formula:



wherein R signifies phenyl or naphthyl which may be substituted with lower alkyl or lower alkoxy groups or halogen atoms.

1/4



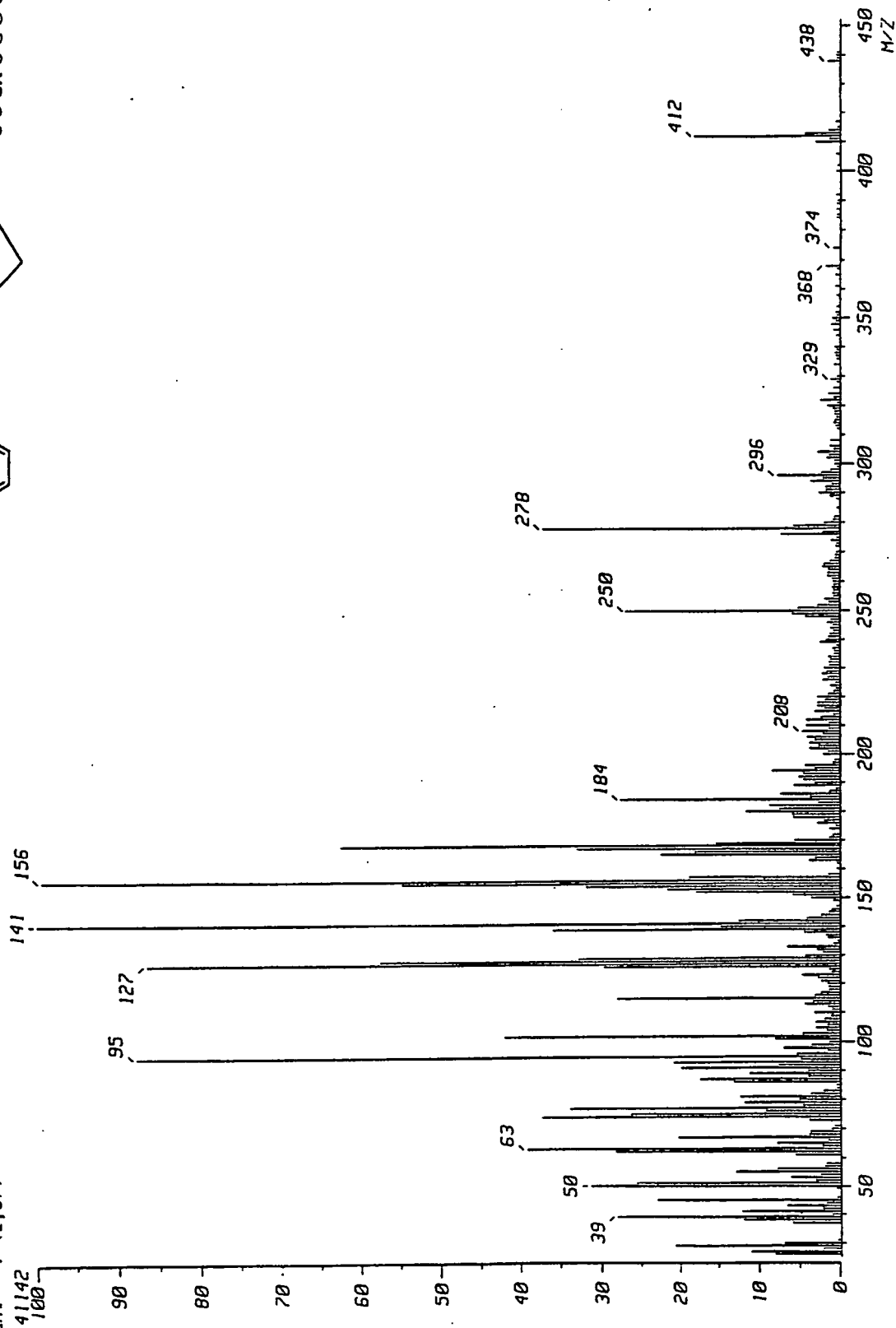
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Fig. 3

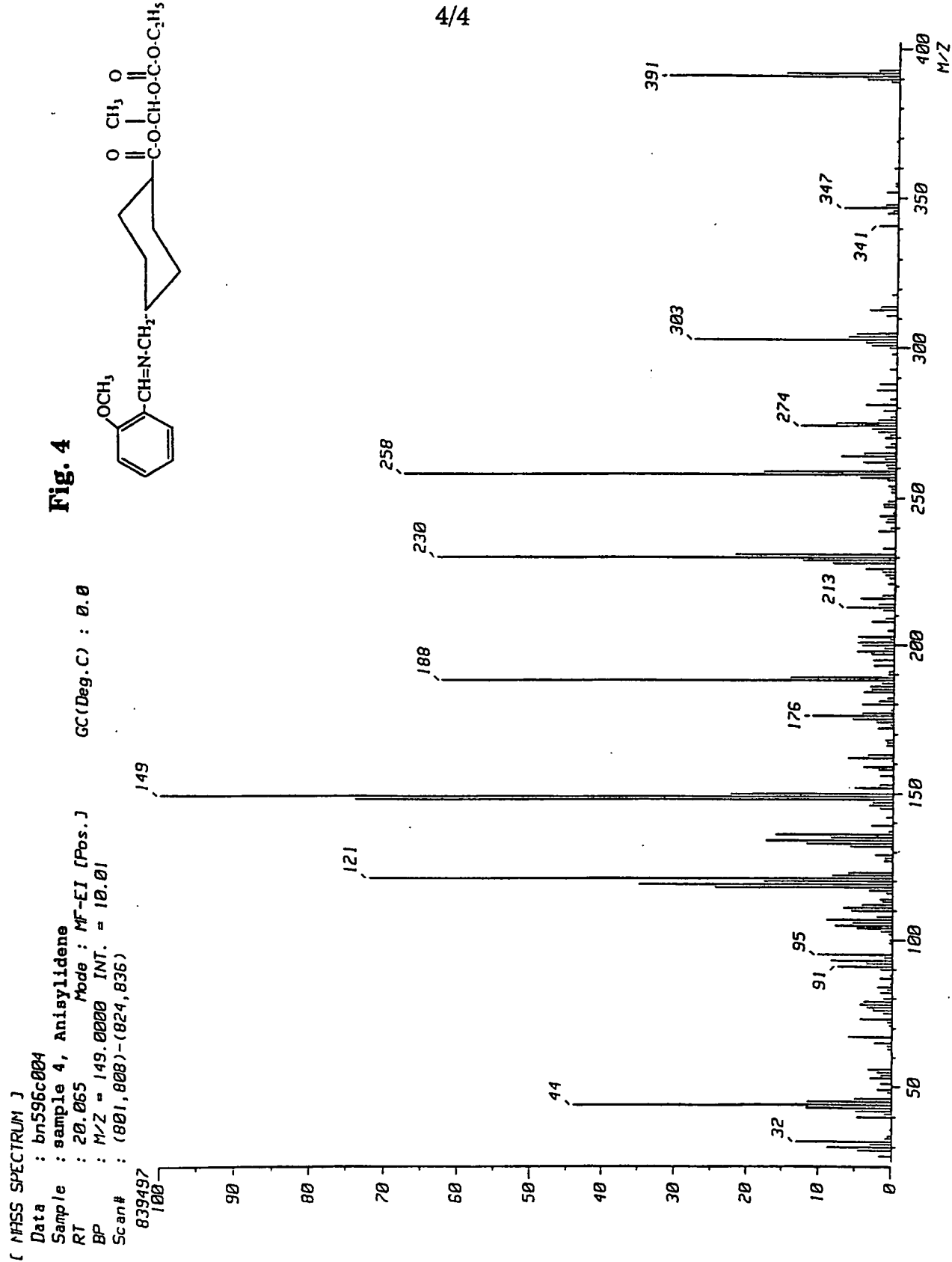
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Sample : sample 5, naphthyl, without matrix
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BP : M/Z = 141.0000 INT. = 0.11
Scan# : (2,37)

DI(Deg.C) : 7.4



SUBSTITUTE SHEET

4/4



SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 93/01115

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07C 229/46, C07C 227/18, C07C 251/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA SEARCH, CHEMNAME

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP, A1, 0079872 (KABIVITRUM AB), 25 May 1983 (25.05.83), example 3 and the claims ---	1-4
Y	EP, A2, 0041826 (KUREHA KAGAKU KOGYO KABUSHIKI KAISHA), 16 December 1981 (16.12.81), example 6 and the claims -----	1-4

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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"E" earlier document but published on or after the international filing date

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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

29 March 1994

Date of mailing of the international search report

07-04-1994

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INTERNATIONAL SEARCH REPORT
Information on patent family members

26/02/94

International application No.
PCT/SE 93/01115

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0079872	25/05/83	SE-T3- 0079872 CA-A- 1202637 JP-C- 1665602 JP-B- 3026183 JP-A- 58092611 US-A- 4483867	01/04/86 19/05/92 10/04/91 02/06/83 20/11/84
EP-A2- 0041826	16/12/81	SE-T3- 0041826 AU-B- 542972 AU-A- 7116881 CA-A- 1183150 JP-A- 57116035 US-A- 4377594 AU-B- 538938 CA-A- 1183151 EP-A,B- 0041827 SE-T3- 0041827	28/03/85 17/12/81 26/02/85 19/07/82 22/03/83 06/09/84 26/02/85 16/12/81